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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,380	03/29/2002	Izumu Saito	1422-0527P	2374

2292 7590 06/09/2004

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,380	SAITO ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 18* is/are rejected.

7)☒ Claim(s) *9 and 11-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/02*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 29 March 2002 as the US national stage of international application PCT/JP00/06686, filed 28 September 2000, which claims benefit of Japanese patent applications 11-280210, filed 30 September 1999, and 11-346727, filed 6 December 1999.

The preliminary amendments filed 29 March 2002 and 3 July 2002 have been entered. Claims 1-20 were originally filed. Claims 4, 8, 13-16, 18 and 19 were amended in the 29 March amendment and claim 1 was amended in the 3 July amendment. Claims 1-20 are presently pending.

Election/Restrictions

Applicant's election of Group I in the Paper filed 28 April 2004 and the mutant FRT sequence set forth as SEQ ID NO: 2 in the interview of 7 May 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 19 and 20 and the mutant FRT sequences set forth as SEQ ID NO: 3-5 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention.

Claims 1-18 are presently under consideration.

Claim Objections

Claims 9 and 11-17 objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim (*i.e.*, the multiple dependent claim 9 depends from the multiple dependent claim 3, and claims 11-17 depend from claim 9). See MPEP § 608.01(n). Accordingly, the claims 9 and 11-17 have not been further treated on the merits.

Claims 5-7 and 10 are objected to because of the following informalities: The use of the preposition "at" in the phrase "at between" in claims 5 and is grammatically incorrect. Likewise, the phrase "different sequences in each other", which appears in claims 6, 7 and 10, does not make grammatical sense. It seems that Applicant intends that the sequences are different relative to one another and amending the claims accordingly would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 and 18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-7, as written, do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. Claims 1-7 are directed to DNA's comprising mutant FRT sequences which are based on an FRT sequence that occurs

naturally in the yeast 2 μ DNA. As mutations also occur naturally, the mutant FRT sequences of the claims could arise spontaneously, absent the hand of man. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, *e.g.*, by insertion of "isolated" or "purified". See MPEP 2105.

Claim 18 is directed to a transgenic animal carrying a mutant FRT sequence on chromosomes. As the specification does not define "transgenic animal" in such a way as to exclude humans from the scope of the claim, the claim encompasses a transgenic human, which is non-statutory subject matter. The Examiner can find no support in the specification for a subgenus or species of transgenic animal that excludes humans.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for replacing a gene wherein the method steps set forth in the claim are practiced *in vitro*, does not reasonably provide enablement for the method practiced *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claim is directed to a method for replacing a gene in a nucleic acid involving site-specific recombination mediated by FRT sequences flanking the gene to be inserted. The method steps generally encompass the method practiced in a test-tube or cultured cells (*i.e.*, *in vitro*) or in whole animals (contemplated, *inter alia*, at pages 22-23 and pages 30-33). With regard to using the method practiced *in vivo*, the specification teaches that genes can be introduced into a transgenic animal, presumably for research purposes (see, *e.g.*, the first full paragraph on page 23), or into a human that has been pretreated with a vector containing FRT sequences, in which case the method is alleged to have therapeutic utility.

As the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation (see *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513), the disclosure must enable the skilled artisan to practice the claimed method *in vivo* such that it can be used as contemplated in the specification.

State of the prior art and level of predictability in the art: Upon reviewing the art, the Examiner is unable to find a single working example of *in vivo* gene replacement using the FLP recombinase system. Although two reports of *in vivo* gene deletions using FRT repeats flanking a gene were available in the art at the time of filing (*i.e.*, Dymecki (1996) *Proc. Natl. Acad. Sci. USA* 93:6191-619 and Vooijs *et al.* (1998) *Oncogene* 17:1-12), there are no examples of a method wherein a gene was inserted into a genome *in vivo* using FLP recombinase. The art is silent with regard to failed attempts at practicing a method according to the instant claims; however, one of ordinary skill in the art would reasonably expect that the efficiency of a method requiring only a single intramolecular recombination (*i.e.*, deletion of a gene as demonstrated in the art) would be much higher than the efficiency of a method that requires two recombination events between two separate molecules. Thus, the limited success in applying FRT recombinase to obtaining *in vivo* gene deletions does not reasonably support enablement for a method that is logically much less efficient. Therefore, the skilled artisan is solely dependent upon the teachings of the specification to provide full, clear, concise, and exact guidance as to how the claimed method can be practiced *in vivo* such that a useful phenotypic effect can be obtained.

With regard to therapeutic application of the claimed method, the art teaches that, beyond merely obtaining successful gene replacement, there are many obstacles that must be overcome before a gene therapy method is enabled. At the time of filing, gene therapy utilizing the administration of recombinant nucleic acids, regardless of the mode of delivery was considered to be highly unpredictable. Verma et al. states, "[t]he Achilles heel of gene therapy is gene delivery...", and, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph

2). Marshall concurs, stating, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, "... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's

compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

In an article published well after the effective filing date of the instant application, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches that the problems described above remained unsolved at the time the instant application was filed. Rubanyi states, "[a]lthough the theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far..." (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see especially "**3. Technical hurdles to be overcome in the future**", beginning on page 116 and continued through page 125). Thus, the art

clearly establishes that, at the time of filing, expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art was very low.

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The specification does not identify any particular disease to be treated by the contemplated methods. However, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In

subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels. Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660). Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using the method disclosed in the instant application was extremely low at the time of filing.

Amount of direction provided by the inventor and existence of working examples: The working examples provided in the instant specification are limited to assays performed in test tubes using cell extracts. With regard to practicing the claimed method *in vivo*, the teachings of the specification are merely general recitations of what was already available to the skilled artisan a the time of filing.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, practicing the claimed invention *in vivo* would clearly require experimentation beyond what is routine in the art. It cannot be said that developing a technology demonstrated to be effective in a cell free extract such that it can be used *in vivo* is routine if the technology has never been practiced successfully *in vivo*. In the instant case, the art is silent with regard to applying FLP recombinase mediated gene replacement to obtain a useful, or even measurable, phenotypic change in an animal. The instant disclosure provides mutant FRT sequences having essentially the same activity as the FRT sequences that were known in the art at the time of filing and general teachings directed to making transgenic animals and therapeutic gene replacement. Given that the teachings provided are no different than what was already available to the skilled artisan at the time of filing, the art recognized unpredictability of obtaining gene replacement of sufficient degree to provide a useful effect and the absence of any working examples of the *in* vivo application of the claimed invention even 5 years after the effective filing date of the application, practicing the claimed

invention commensurate with its full scope would clearly require experimentation beyond what is considered routine in the art.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured cell, does not reasonably provide enablement for a cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of the invention and Breadth of the claims: The claims are directed to a cell transformed with a mutant FRT sequence. As the specification contemplates cells in transgenic animals and cells in genetically modified humans (*Id.*) the disclosure must teach the skilled artisan how to use cells *in vivo*. However, as described in detail herein above, the specification fails to provide an enabled *in vivo* method of using the claimed invention. Beyond that, there is no readily apparent use for the claimed cell *in vivo*.

State of the prior art and level of predictability in the art: To the extent that the cell of the claim is comprised within a transgenic animal, the animal would have no distinct phenotypic characteristics and, although the genome of the animal would comprise nucleic acid sequences that are not found in wild type animals, the skilled artisan would not expect to be able to use the animal as asserted in the specification without undue experimentation. Further, the animal of the claims encompasses any species of animal and practicing the invention would require expression of a functional FLP recombinase such that efficient gene replacement could be achieved. However, the art teaches that many of the phenotypes examined in transgenic and knockout animas are influenced by the genetic background in which they are studied and the effect of

allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). Thus, even if one were to be in possession of a single species of animal that was use according to the teachings of the specification, this success would not be predictive of success in any other species of animal.

Amount of direction provided by the inventor and existence of working examples: As described above, the working examples provided in the instant specification are limited to assays performed in test tubes using cell extracts. Teachings beyond that scope are merely general recitations of technologies that were already available to the skilled artisan at the time of filing or are prophetic.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the specification fails to provide an enabled use for the claimed cell *in vivo*. As stated above, it cannot be said that developing a technology demonstrated to be effective in a cell free extract such that it can be used *in vivo* is routine if the technology has never been practiced successfully *in vivo*. Given that the teachings provided are no different than what was already available to the skilled artisan at the time of filing, the art recognized unpredictability of obtaining gene replacement of sufficient degree to provide a useful effect and the absence of any working examples of the *in* vivo application of the claimed invention even 5 years after the effective filing date of the application, using the claimed cell *in vivo* would clearly require experimentation beyond what is considered routine in the art.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. For reasons provided herein above, the subject matter of claim 18, which is directed to a transgenic animal comprising at least one wild type FRT sequence and at least one mutant FRT sequence is not enabled over any scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 3, 6, 7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in the statement, "the mutant FRT sequence consists of a sequence further comprising substitutions of at least one nucleotide in a region other than the spacer region in the mutant FRT sequence defined in claim 1." It is not clear whether the claimed mutant FRT sequence is limited to comprising the spacer region of the mutant FRT sequence of claim 1. According to the claim, the mutant FRT sequence must further comprise substitutions in a region other than the spacer defined in claim 1, but there is no positive statement as to what else must be comprised within the mutant FRT sequence. Therefore, the claim would seem to read on any mutant FRT sequence that does not comprise the spacer region defined in claim 1 as well as those that do comprise the spacer and substitutions in a region other than the spacer.

Claims 3, 6, 7 and 10 are indefinite insofar as they depend from claim 2.

Claims 6 and 7 are additionally indefinite in the recitation, "two mutant FRT sequences having different sequences in each other defined in claim 3". Claim 3 merely defines a single FRT sequence as being incapable of recombination with another mutant FRT sequence. Thus, the mutant FRT sequences of claim 6 are limited to comprising sequence that is different relative to each other and to being incapable of DNA recombination with at least one other mutant FRT sequence. However, the mutant FRT sequences are not limited to being incapable of recombining with each other because there is no explicit or implicit limitation to that effect. As this would seem inconsistent with the invention as disclosed in the specification, it is unclear whether applicant intends the claim to read as such. Clarification is requested.

Claim 7 is indefinite in depending from claim 6.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 3, 6, 7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Schlake (1994) *Biochem.* 33:12746-12751 or Seibler *et al.* (1997) *Nucleic Acids Res.* 36:1740-1747. The citations were made of record in the IDS filed 29 March 2002.

As discussed herein above under 35 U.S.C. §112, second paragraph rejections, claim 2 has been construed, according to its broadest reasonable interpretation, as encompassing any mutant FRT sequence that does not comprise the spacer region defined in claim 1 as well as

those mutant FRT sequences that comprise the spacer region defined in claim 1 and mutations outside of that region.

In Table 1, Schlake *et al.* discloses several mutant FRT sequences comprising substitutions in a region other than in the spacer region in the mutant FRT sequence defined in claim 1. Thus Schlake *et al.* anticipates the subject matter of claim 2.

Schlake *et al.* further teaches the mutant FRT sequence of claim 2 wherein: no specific recombination reaction is obtained with another mutant FRT sequence having sequence different therefrom according to claim 3 (see especially Figure 3 and the caption thereto, and the first paragraph on page 12750);

a DNA comprising at least two mutant FRT sequences comprising distinct sequences relative to one another according to claim 6 (see especially the concluding sentence of the first paragraph on page 12750);

the DNA of claim 6 in which the mutant FRT sequences flank a desired gene according to claim 7 (see especially Figure 3 and the caption thereto); and

a method for replacing a gene wherein a DNA comprising two mutant FRT sequences comprising distinct sequences relative to one another and flanking a gene A is reacted with another DNA comprising two mutant FRT sequences comprising distinct sequences relative to one another and flanking a gene B according to claim 10 (see especially Figure 2 and the caption thereto).

Seibler *et al.* cites the F_3 and F_5 mutant FRT sequences of Schlake *et al.* which comprise substitutions in a region other than in the spacer region in the mutant FRT sequence defined in

claim 1 (*Id.*; see especially the second full paragraph on page 1741 of Seibler *et al.*). Thus, Seibler *et al.*, like Schlake *et al.*, anticipates the subject matter of claims 2 and 3.

Seibler *et al.* further teaches a DNA comprising at least two mutant FRT sequences comprising distinct sequences relative to one another according to claim 6, the DNA of claim 6 in which the mutant FRT sequences flank a desired gene according to claim 7, and a method for replacing a gene wherein a DNA comprising two mutant FRT sequences comprising distinct sequences relative to one another and flanking a gene A is reacted with another DNA comprising two mutant FRT sequences comprising distinct sequences relative to one another and flanking a gene B according to claim 10 (see especially Figure 1 and the caption thereto).

The nucleic acids and method of replacing a gene disclosed in the prior art is the same as the nucleic aids and method claimed in the instant application; therefore, the claims are anticipated by the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DMS

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER